Europäisches Patentamt
European Patent Office
Office européen des brevets

Bescheinigung Certificate Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

02024744.1

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

Europäisches Patentamt | Eur[illegible] Patent Office | Office européen des brevets

Anmeldung Nr:
Application no.: 02024744.1
Demande no:

Anmeldetag:
Date of filing: 06.11.02
Date de dépôt:

Anmelder/Applicant(s)/Demandeur(s):

MEDIVIR AB
Lunastigen 7
S-144 44 Huddinge
SUEDE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Synergistic interaction of abacavir and alovudine

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s) revendiquée(s)
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation/International Patent Classification/
Classification internationale des brevets:

A61K31/00

Am Anmeldetag benannte Vertragstaaten/Contracting states designated at date of filing/Etats contractants désignées lors du dépôt:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LU MC NL PT SE SK TR

Synergistic interaction of abacavir and alovudine

Technical Field

This invention relates to the unexpected level of synergy exhibited between the HIV and HBV antivirals alovudine and abacavir against multiresistant HIV. The invention provides novel pharmaceutical preparations comprising the two agents in admixture or separately for concomitant or sequential administration and methods of treatment involving them.

Background to the Invention

Alovudine (3'-deoxy-3'-fluorothymidine, FLT) is described in WO88/00088 as an antiviral active against HIV and HBV. Alovudine is a prodrug which is converted in vivo to the active triphosphate.

Abacavir (1R,4S)-9-[4-(hydroxymethyl)-2-cyclopenten-1-yl]guanine, carbovir is described in EP 0434450 as having potent activity against HIV and HBV. Abacavir is also a prodrug which is converted in vivo to the active triphosphate.

Alovudine and abacavir have each exhibited modest synergy with certain selected nucleosides, especially in in vitro tests (see for example US 5,571,798 and WO 00/16779). However, we have now discovered in the clinical context that the particular combination of alovudine and abacavir produces a degree of antiviral synergy which is significantly greater than the usual level of synergy shown by the respective active agent.

Brief description of the invention

A first aspect of the invention provides a pharmaceutical preparation comprising a synergistic combination of abacavir and alovudine and a pharmaceutical carrier therefor.

A further aspect of the invention provides the use of abacovir and alovudine together for the treatment of HBV or especially multiresistant HIV, wherein the use comprises combined, concomitant or sequential administration of alovudine and abacovir.

The invention further provides a patient pack comprising alovudine and/or abacavir and an information insert containing directions on the use of both alovudine and abacavir together in combination.

The unexpectedly profound degree of antiviral synergy of the invention provides such benefits as more complete viral suppression, viral suppression over longer periods, limits the emergence of drug-escape mutations and thus the development of multiresistant HIV and HBV and allows better management of drug related toxicities. The use of this drug combination may, in some circumstances decrease the number of pills taken by the patient and therefore increase patient compliance.

It will be appreciated that the alovudine and abacavir combination of the invention may be administered simultaneously, either in the same or different pharmaceutical composition, or sequentially. In the case of sequential administration, the delay in administering the second active ingredient should not be such as to lose the synergistic benefit of the invention. Typically sequential administration will not involve delays of greater than 12 hours, preferably less than 1 hour, such as before and after a meal.

Due its good tolerability, once day dosing and very small dosage/day, alovudine can advantageously be administered as an add-on to existing HAART regimes, such as therapies comprising one or two nucleoside analogues and a protease inhibitor and/or one or more NNRTIs. Such permutations can be chosen from conventional HIV antivirals such as 3TC, DDI, nevirapine, delavirdine, efavirenz, ritonavir, kaletra, saquinavir, amprenavir, amprenavir phosphate, indinavir etc. Preferably the preexisting regime or concomitant antiviral does not include d4T.

For ease of administration the alovudine and abacavir are conveniently presented in the same unit dosage form, such as a capsule or tablet or in a fluid containing appropriate concentrations of the two active agents.

The amount of alovudine and abacavir necessary for suppression of HIV or HBV will, of course vary from patient to patient and is ultimately at the discretion of the medical practitioner taking account of such well known factors as body weight, route of administration, concomitant medication, ag, gender and general condition and the nature and severity of the disease.

In general abacavir is dosed in the range of about 3 to about 120 mg/kg/day such as 1-90 mg/kg/day, preferably 5-60 mg/kg/day. Preferably the abacavir is present in an amount of 200-800 mg per unit dose, more preferably 300-500 mg per unit dose.

In general alovudine is dosed in the range of about 0.001-0.5 mg/kg/day, preferably 0.005-0.15 mg/kg/day. Favoured regimes thus include 0.01-0.5 mg/kg/day, such as 0.05-0.12 mg/kg/day. Preferably the alovudine is present in an amount of 0.1-20 mg per unit dose, such as 0.5-10 mg per unit dose, especially 0.5-5 mg/unit dose, such as 2-5 mg per unit dose.

Alovudine and abacavir are conveniently administered once or twice a day, especially once per day.

The alovudine and abacavir are conveniently administered and/or presented in a weight ratio corresponding to their respective ED_{50}, for example in the ratio 1-10:200-800

Abacavir is commercially available and its production is extensively described in the patent and academic literature. Alovudine is conveniently prepared as described in EP 495 225 and EP 470 355.

Abacavir and alovudine, particularly at the dosage rates herein described, are readily formulated in conventional pharmaceutical carriers and with

conventional excipients. The compounds of the invention are particularly suited to oral administration, but may also be administered rectally, vaginally, nasally, topically, transdermally or parenterally, for instance intramuscularly, intravenously or epidurally. The compounds may be administered alone, for instance in a capsule, but will generally be administered in conjunction with a pharmaceutically acceptable carrier or diluent. The invention extends to methods for preparing a pharmaceutical composition comprising bringing alovudine and abacovir in conjunction or association with a pharmaceutically acceptable carrier or vehicle.

Oral formulations are conveniently prepared in unit dosage form, such as capsules or tablets, employing conventional carriers or binders such as magnesium stearate, chalk, starch, lactose, wax, gum or gelatin. Liposomes or synthetic or natural polymers such as HPMC or PVP may be used to afford a sustained release formulation. Alternatively the formulation may be presented as a nasal or eye drop, syrup, gel or cream comprising a solution, suspension, emulsion, oil-in-water or water-in-oil preparation in conventional vehicles such as water, saline, ethanol, vegetable oil or glycerine, optionally with flavourant and/or preservative and/or emulsifier.

Brief description of the drawings

An embodiment of the invention will be illustrated by way of example only with reference to the drawings in which:

Figure 1 depicts median reduction in viral load in patients treated with the synergistic combination of the invention comprising alovudine added to an abacovir-containing regimen; in contrast to patients treated with alovudine and a non-abacovir-containing regimen

Figure 2 depicts reduction in viral load in a comparative experiment in which an alovudine /ddI-containing regimen is plotted beside an alovudine/non-ddI regimen.

Detailed description of the invention

A phase IIa trial was performed with 15 patients failing their current NRTI-containing regimens. Each patient had HIV RNA > 1000 cp/ml, with at least 2 mutations in the viral RT induced by previous viral therapy, as established by genotypic assay. Patients had a baseline viral load of 3.93 $\log_{10}$ cp/ml.

The patients were administered qd 7.5 mg alovudine in a conventional carrier in addition to their current regimen for four weeks. The current regimes included various permutations of 3-5 HIV antivirals selected from 3TC, DDI, D4T, nevirapine, DMP, ritonavir, kaletra, saquinavir, amprenavir and indinavir, administered in their conventional dosage forms and regimens. Antiviral load evaluation was performed weekly and then four weeks after discontinuation of alovudine. The alovudine addition was generally well tolerated and there was no withdrawal from therapy and no serious adverse events. A transient mean increase in CD4 counts of +52 councts/mm^3 was detected.

The results are plotted in Figures 1 and 2. Referring initially to Figure 1, it will be apparent that the alovudine/abacovir-containing regimen results in significantly lower median viral loads compared to patients administered with alovudine but whose concomitant regimen did not include abacovir. This profound reduction in viral load with alovudine/abacovir of the invention is surprising when contrasted with the performance of alovudine and ddI (didanosine) regimes in Figure 2, plotted against non-DDI containing regimens. Alovudine and ddI show clear synergy in *in vitro* tests (Cox et al AIDS Res Hum Retrovir. 1994 (12):1275-9). As is seen in Figure 2, this known synergy translates in the clinical setting to a 0.2-0.3 log reduction. In contrast the combination of the invention consistently resulted in 1-1.5 log recuctions, which is a quantum jump in synergy bearing in mind the logarithmic scale used.

As this clinical trial was performed as an add-on therapy to the patients pre-existing regime, it will be appreciated that the alovudine qd was administered in a separate dosage form to the abacovir (typically bd) and other antivirals (typically administered 2-4 times per day)

Claims

1. A pharmaceutical preparation comprising a synergistic combination of abacavir and alovudine and a pharmaceutical carrier therefor.

2. A preparation according to claim 1 wherein the alovudine is present in an amount of 1-10 mg per unit dose.

3. A preparation according to claim 2 wherein the alovudine is present in an amount of 0.5-7.5 mg per unit dose.

4. A preparation according to claim 3 wherein the alovudine is present in an amount of 0.5-5 mg per unit dose.

5. A preparation according to claim 1, wherein the abacavir is present in an amount of 200-800 mg per unit dose.

6. A preparation according to claim 5, wherein the abacavir is present in an amount of 300-500 mg per unit dose.

7. A preparation according to claim 1, wherein the alovudine and abacavir are present in a weight ratio corresponding to their respective ED_{50}.

8. A preparation according to claim 1, wherein the alovudine and abacavir are present in the ratio 1-10:200-800

9. A patient pack comprising alovudine and/or abacavir and an information insert containing directions on the use of both alovudine and abacavir together in combination.

10. Use of abacovir and alovudine together for the treatment of multiresistant HIV, wherein the use comprises simultaneous, combined or sequential administration of alovudine and abacovir.

11. Use according to claim 10, wherein the use comprises administration of a preparation as defined in any one of claims 1-8 or the patient pack of claim 9.

Abstract of the Disclosure

The nucleoside analogues alovudine and abacavir show unexpectedly profound antiviral synergy when coadministered to HIV-infected patients in combination or sequentially.

1/2

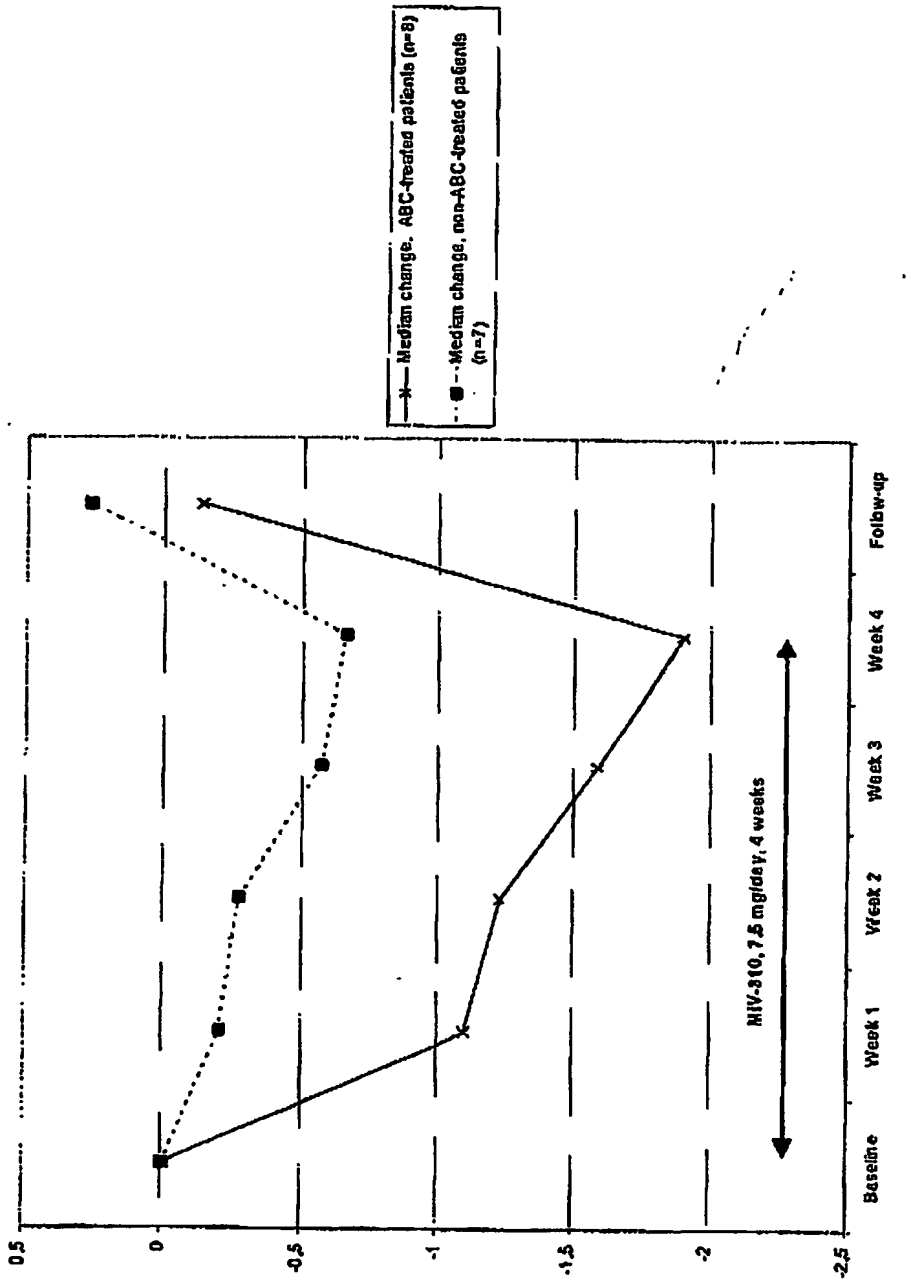

FIGURE 1

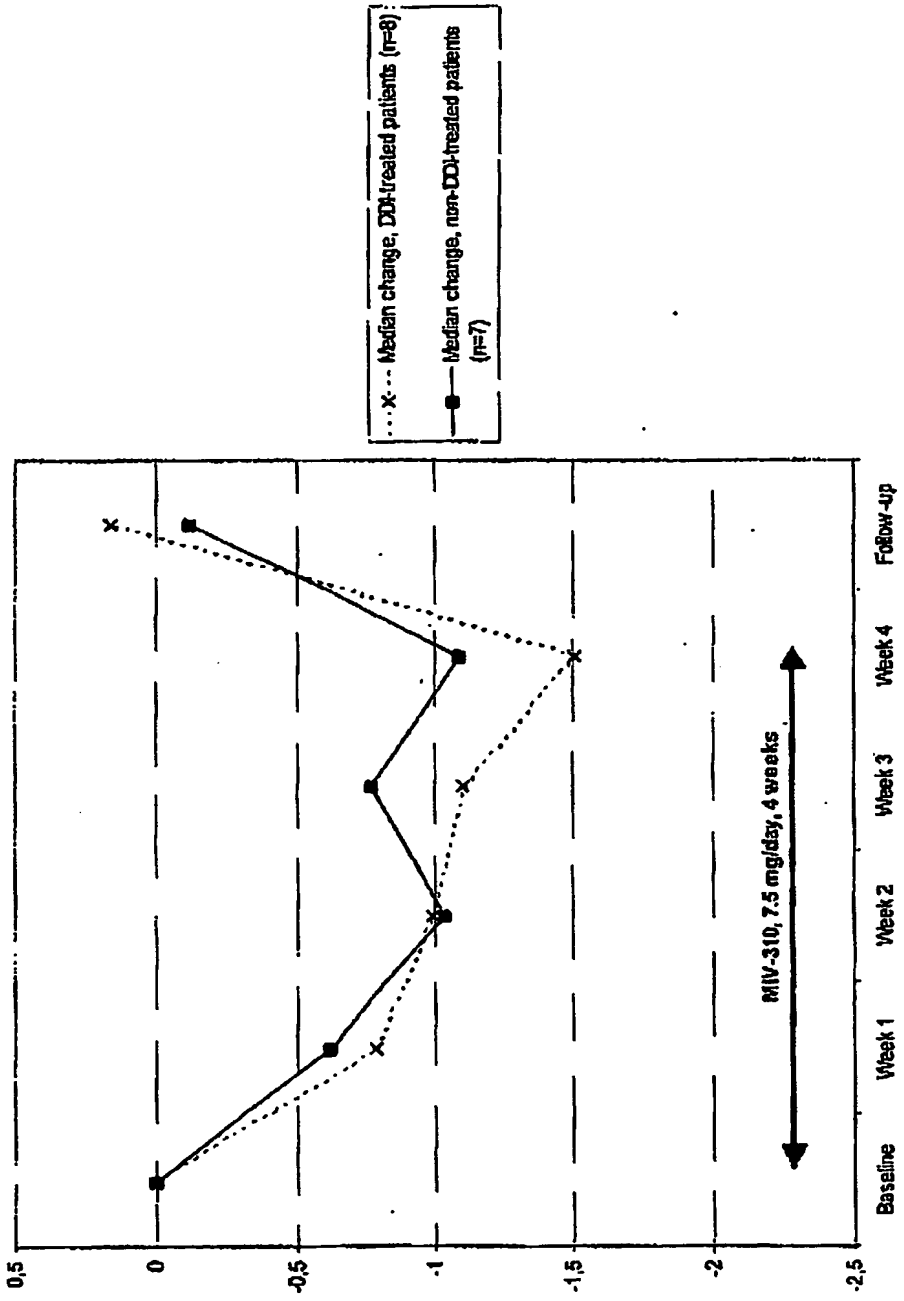
Median change, DDI-treated patients (n=8)
Median change, non-DDI-treated patients (n=7)
0,5
0
-0,5
-1
-1,5
-2
-2,5
Baseline
Week 1
Week 2
Week 3
Week 4
Follow-up
MIV-310, 7.5 mg/day, 4 weeks

FIGURE 2